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RESEARCH

When to remeasure cardiovascular risk in untreated people at low and intermediate risk: observational study

 OPEN ACCESS

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Abstract

Objective To estimate the probability of becoming high risk for cardiovascular disease among people at low and intermediate risk and not being treated for high blood pressure or lipid levels.

Design Observational study.

Setting General communities in Japan and the United States.

Participants 13 757 participants of the Tokyo health check-up study and 3855 of the Framingham studies aged 30-74 years with complete data on risk equation covariates, not receiving blood pressure or cholesterol lowering treatment, and with an estimated risk of cardiovascular disease <20% within 10 years. We stratified participants on the basis of baseline risk: <5%, 5-<10%, 10-<15%, and 15-<20%. We used follow-up measurements from the Tokyo study done annually over three years (2006-10) and follow-up visits in the Framingham study done between eight (1968-75) and 19 years (1990-1995) after baseline.

Main outcome measure Estimated 10 year risk of a cardiovascular event >20% using the Framingham equation.

Results At baseline most participants had <5% risk (60.6% of Tokyo cohort and 45.7% of Framingham cohort) or 5-<10% risk (24.0% and 28.0%, respectively) of a cardiovascular event within 10 years. There was <10% probability of crossing the treatment threshold at 19, 8, and 3 years for baseline risk groups <5%, 5-<10%, and 10-<15%, respectively, and >10% probability of crossing the treatment threshold at one year for the 15-<20% baseline risk group.

Conclusions Decisions on the frequency of remeasuring for cardiovascular risk should be made on the basis of baseline risk. Repeat risk estimation before 8-10 years is not warranted for most people initially

not requiring treatment. However, remeasurement within a year seems warranted in those with an initial 15-<20% risk.

Introduction

Clinical guidelines increasingly recommend starting therapy to lower blood pressure or cholesterol on the basis of an individual's overall absolute risk of cardiovascular disease¹⁻⁶ using risk prediction scores such as the Framingham equation.⁷ For example, in the United Kingdom, clinicians are advised to start treatment for patients with an estimated 10 year risk of cardiovascular disease that is 20% or greater,^{3 4} whereas in Europe the treatment threshold is an estimated 10 year risk of fatal cardiovascular disease of 5% or greater.⁵ Guidelines in the United States use a threshold of 20% risk of cardiovascular disease over 10 years as part of a decision algorithm for recommending cholesterol lowering treatment⁸ but do not currently use absolute risk for recommending blood pressure lowering treatment.⁹ Updated guidelines for the treatment of raised blood pressure, cholesterol level, and obesity, as well as an "integrated cardiovascular risk reduction" guideline are being formulated under the direction of the National Heart, Lung, and Blood Institute.¹⁰ Other countries, such as Australia and New Zealand, use an estimated five year risk of cardiovascular disease of 15% as the recommended treatment threshold.^{1 2}

For those who do not meet the treatment threshold, guidelines differ in their recommendations for repeat risk estimation. In people at low risk (<10% 10 year risk, <5% five year risk) of cardiovascular disease repeat estimation is recommended at least every two years,¹¹ five years,^{3 4} or 5-10 years²; for people

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Supplementary material

at intermediate risk (10-20% 10 year risk, 5-15% five year risk) of cardiovascular disease repeat estimation is recommended every 3-6 months,⁶ 6-12 months,¹¹ or five years.²⁻⁴ The European guidelines do not recommend a monitoring interval at all for any risk group.⁵ This lack of uniformity in guidance reflects an absence of evidence on optimal timing of repeat risk estimation, with expert opinion informing recommendations instead. Repeat risk estimations that are more frequent than necessary waste scarce health resources resulting from more clinic visits and unnecessary laboratory tests. There is also an increased likelihood of false positive test results, where people are wrongly identified as being at high risk (>20% 10 year risk). Such people may start unnecessary treatment, be subjected to more tests and even more frequent follow-up, and experience the psychological distress from being labelled at high risk of a cardiovascular event.

Using data collected in two large observational studies we estimated the probability of crossing a treatment threshold of 20% 10 year risk for those initially below this threshold.

Methods

To assess risk estimation across a wide breadth of time, we used two cohorts: the Tokyo health check-up study, of medium duration (1-3 years), and the Framingham studies of longer duration (8-19 years). In both cohorts low proportions of participants were taking drugs to lower blood pressure or cholesterol levels, which enabled observation of the natural progression of untreated cardiovascular risk over time.

Tokyo health check-up study

The selection of participants in the Tokyo health check-up study has been described previously.¹² We included participants who first attended the health check-up programme at the Centre for Preventive Medicine, St Luke's International Hospital, Tokyo, Japan between January 2005 and December 2007. Around 80% of the participants and their dependents are employees of various companies and local government organisations in Tokyo and costs are paid for by the employer. The remaining 20% of participants are citizens of Tokyo who individually registered for the programme and paid for it without company sponsorship. Participants were eligible for the current study if they were screened at least four times in 2005-10, were aged 30 to 74 years, had complete data on risk equation covariates, were not receiving treatment to lower blood pressure or cholesterol levels, and had an estimated risk of cardiovascular disease within 10 years that was less than 20% (using the Framingham equation⁷). Of a total 75 790 people who met these eligibility criteria and who attended the baseline visit, we excluded 62 033 because they did not attend all three subsequent annual follow-up visits. The resulting study sample had 13 757 participants. Table 4 in the supplementary file compares those who were included with those who were excluded. No important differences were observed between the two groups.

Framingham study

The design and selection criteria for the original Framingham Heart Study and the Framingham Offspring Study have been described previously.^{13 14} Participants were eligible for the present study if they were free from cardiovascular disease when attending the 11th examination visit of the original cohort (1968-71), or the first (1971-75) examination visit of the offspring cohort, were aged 30 to 74 years, had complete data on risk equation covariates, were not receiving treatment to lower blood pressure or cholesterol levels, and had an estimated

risk of cardiovascular disease within 10 years that was less than 20% (using the Framingham equation⁷). The resulting study sample had 3855 participants.

Follow-up

For both studies, follow-up visits were used where data were available to allow calculation of cardiovascular risk. For the Tokyo study this was approximately yearly visits between 2005 and 2010. For the Framingham Heart Study, this was the 15th (1977-79) and 20th (1986-90) examination visits, and for the offspring study this was the second (1979-83), third (1983-87), fourth (1987-91), and fifth (1991-95) examination visits. Those who developed cardiovascular disease during the period of follow-up without crossing the treatment threshold were omitted from the analysis at later time points.

Measurement of risk factors

In the Tokyo study, blood pressure measurements were taken in the sitting position by trained nurses; blood pressure measurements were made twice, once after sitting quietly for several minutes and then again after at least two minutes. The average of the two readings was recorded as the participant's blood pressure. A fully automatic calibrated oscillometric blood pressure measuring device (BP-203 RV II, Colin, Japan) was used with a standard arm cuff. In Framingham, blood pressure measurements were made on the left arm of the seated participants with a mercury column sphygmomanometer and an appropriately sized cuff; the average of two doctor obtained measures constituted the examination blood pressure.

In both studies serum total and high density lipoprotein cholesterol levels were determined with standardised enzymatic methods. Cigarette smoking status was ascertained by self report. Diabetes was defined as fasting glucose ≥ 126 mg/dL¹⁵ or use of insulin or oral hypoglycaemic drugs. Blood pressure and cholesterol lowering treatment was based on self report (Tokyo and Framingham) and ascertained by the doctor examiner at the heart study (Framingham¹⁶).

Statistical analysis

For each individual we calculated their estimated risk of cardiovascular disease within 10 years (based on the Framingham risk equation⁷) at each time point. Where the measurement of systolic blood pressure (90-200 mm Hg), high density lipoprotein cholesterol (10-100 mg/dL), or total cholesterol (100-405 mg/dL) fell outside of the ranges used by the Framingham online risk calculator, we used the minimum or maximum limit as is recommended.¹⁷ To deal with the problem of ages outside of the recommended range, we did additional analyses restricted to people who were aged 74 years or less at the final follow-up visit.

Some people started treatment during the follow-up period, which may have partially negated the increase in risk that would otherwise have occurred. To allow for this, we estimated their blood pressure or cholesterol level subsequent to the time treatment was started by adding the mean increase in risk found in treatment naive patients to the last risk estimate before the patients started treatment.

We defined four subgroups of people based on baseline risk: <5%, 5-<10%, 10-<15%, and 15-<20% 10 year risk. We calculated the point prevalence of crossing the 20% treatment threshold at time points of 1, 2, and 3 years (Tokyo study) and 8, 12, 16, and 19 years after initial assessment (Framingham study, median follow-up times for data used). We used the point prevalence estimates to plot the estimated probability of crossing

the treatment threshold over time. Within the risk groups, we also conducted analyses stratified by decade of age (30-39 years, 40-49 years, 50-59 years, 60-69 years, and ≥ 70 years), to determine whether the risk of crossing the treatment threshold depended on age independent of baseline risk.

Results

Table 1¹ summarises the baseline characteristics of the two cohorts. At baseline most of the participants in both studies were at very low risk (60.6% and 45.7% of Tokyo and Framingham cohorts, respectively, had $<5\%$ risk) or low risk (24.0 and 28.0% of Tokyo and Framingham cohorts had 5- $<10\%$ risk).

The number of participants who started blood pressure and cholesterol lowering treatment during follow-up in the two studies was generally low, reaching a maximum of around one third of participants in the Framingham study after 19 years of follow-up (see supplementary table 1 for detailed results).

Probability of crossing 20% threshold 1-3 years (Tokyo cohort)

Table 2² displays the probability of people crossing the treatment threshold for the four baseline risk groups. The probability of crossing the treatment threshold was $<1\%$ for both the very low baseline risk ($<5\%$) and the low baseline risk (5- $<10\%$) groups after three years. The probability of crossing the threshold for the intermediate baseline risk (10- $<15\%$) group was $<10\%$ (5.7%, 95% confidence interval 4.5% to 7.0%) at three years, whereas for the high intermediate baseline risk (15- $<20\%$) group it was $>10\%$ at one year (16.1%, 13.4% to 19.0%).

Overall, 79 participants developed cardiovascular disease during the three years of follow-up; of these only three had crossed the 20% threshold before clinical disease.

Probability of crossing 20% threshold 8-19 years (Framingham cohort)

Supplementary figure 1 summarises the number of people with data available for risk estimation at each follow-up visit. For visits at eight and 19 years of follow-up, data were available from both the Framingham Heart Study and the Framingham Offspring Study, but for visits at 12 and 16 years data were only available from the offspring study (and consequently there are fewer participants at these visits).

Table 2 displays the probability of people crossing the treatment threshold for the four baseline risk groups. The probability of crossing the treatment threshold for the very low baseline risk ($<5\%$) group was $<10\%$ at 19 years of follow-up (6.8%, 5.5% to 8.2%). The probability of crossing the treatment threshold for the low baseline risk (5- $<10\%$) group was $<10\%$ at eight years (9.1%, 7.1% to 11.3%). Finally, for the intermediate baseline risk (10- $<15\%$) and high intermediate baseline risk (15- $<20\%$) groups it was $>10\%$ at eight years (32.1%, 27.6% to 36.8% and 73.5%, 67.2% to 79.1%, respectively).

Estimates for the age restricted analysis (<74 years at last follow-up) were similar to those reported above (data not shown). The analysis by decade of age within risk subgroups (see supplementary figure 2) suggests that the interval between remeasurement does not depend strongly on age once allowing for baseline risk.

The figure³ summarises the probability of crossing the 20% treatment threshold across the 19 years of follow-up available from the two cohorts, as well as estimates of measurement

variability from the National Health and Nutrition Examination Survey (see supplementary file for further details on results from this study).

The estimate of variability from the National Health and Nutrition Examination Survey data is based on repeat measurements made over a few weeks where there is unlikely to be any true change in the individual's underlying risk. The considerable variability in risk seen over the short term is possibly due to the measurement error and short term variability in blood pressure and lipid levels, which are then magnified by the multiplicative nature of the Framingham risk equation.

Discussion

Our findings suggest that the decision on when to rescreen people's risk of cardiovascular disease should be decided according to their baseline risk and that for most individuals it may be done at a much longer interval than currently recommended. Less than 10% of those in the lowest baseline risk group ($<5\%$) would be over the risk threshold even at 19 years. Those with low baseline risk (5- $<10\%$) also had a low probability of crossing the treatment threshold early on, with 9% crossing the threshold after eight years. Together these two groups made up over 75% of each study population examined—that is, over three quarters of the population had $<10\%$ baseline risk. It is likely that populations who are not receiving treatment in the wider community will be also concentrated in the very low and low risk end of the risk continuum and so for most patients frequent monitoring is not needed.

The results of the low risk groups contrast with those in the intermediate risk (10- $<15\%$) and high intermediate risk (15- $<20\%$) groups, of whom 32.1% and 73.5% had crossed the threshold by eight years of follow-up, indicating that remeasurement before this time is indicated. The probability of crossing the threshold for the intermediate risk (10- $<15\%$) group was only 5.7% after three years, and so clinicians may choose to wait longer to remeasure risk.

Whereas the probability of crossing the 20% risk threshold increases progressively over years 1 to 3 for the three groups below 15% baseline risk, the probability of crossing the 20% threshold seems to decrease in those at 15- $<20\%$ baseline risk, from 16.1% at one year to 11.3% at three years. We do not think this is biologically plausible and is likely to be a chance finding. For all years a large part of this is likely to be due to measurement variability rather than to a true increase in underlying risk: there is a probability of at least this magnitude (19%) of crossing the threshold if remeasurement is done after only a few weeks (see NHANES estimates in the supplementary file). The examples in supplementary table 2 show how even minor changes in risk factors can change people over the threshold. While it is clear that the high-intermediate risk group warrant closer follow-up than those in the lower risk groups, the optimum time interval for remeasurement remains uncertain.

Comparison with other studies

Although this seems to be the first study on the timing of rescreening of people who are initially below a risk threshold for cardiovascular disease, this echoes previous work that has looked at individual risk factors such as cholesterol, blood pressure, and HbA_{1c}. The mean blood pressure of patients in the PROGRESS (perindopril protection against recurrent stroke study) cohort did not change during the 33 month follow-up.¹⁸ However, random drift of patients did vary around this average: by the 33 months around 20% may have had a true increase (or

decrease) of at least 10 mm Hg, suggesting that monitoring every 2-3 years might be reasonable. Similarly, in a six year follow-up of the LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease) trial patients, there was only a slow average increase in lipid levels, but the variation between patients might warrant remeasurement every three years.¹⁹ For both blood pressure and cholesterol levels, modelling suggested that the appropriate interval depended on how close the current level was to an action threshold that might warrant further treatment. This relation to initial level was empirically confirmed in a large Japanese cohort, which showed that the chance of crossing a risk factor threshold depended strongly on the initial level for cholesterol,¹² blood pressure,²⁰ and HbA_{1c}.²¹ Although these studies used different methods and are not directly comparable, the appropriate intervals for reassessing risk of cardiovascular disease seem to be even longer.

Strengths and weaknesses of this study

Although the findings here are likely to be reasonably robust (based on a large group of people with little drop-in to treatment and covering a long duration) there are some weaknesses and limitations. Firstly, our findings are based on two different cohorts with differing lengths of follow-up. The gap in follow-up between data from the two studies (no measurements are available between three and eight years of follow-up) makes it difficult to know when those with 15-20% baseline risk first cross the treatment threshold with a greater probability than that due to measurement variability. Secondly, the estimated proportion of individuals above threshold was based on those who attended each clinic visit. The Japanese cohort was selected in a way such that all participants attended each of the three annual follow-up visits; however, in the Framingham cohort participants were missing at each of the follow-up visits. Those who fail to attend follow-up may be at higher risk of crossing the threshold than those who do attend. As follow-up in the Framingham study is likely to be at least as good as in clinical practice, our estimates for probability of crossing the threshold over the longer term may be generalised to the clinical setting. Thirdly, the small numbers in the higher risk groups mean that our estimates have greater uncertainty than with the group at low initial risk of cardiovascular disease. Although the Framingham and Japanese cohorts seem reasonably consistent, the generalisability across countries and subgroups is uncertain and verification in other cohorts is warranted. Finally, we have only focussed on the intervals between measurement of absolute risk for the purposes of initiating drug treatment. Other intervals may be more appropriate for the assessment of patients for the purposes of assessing the need for intensifying lifestyle modifications, such as weight loss and smoking cessation.

Conclusions

The assessment of absolute cardiovascular risk has become an important guide for when to initiate preventive drug treatments. However, there has been little discussion or work on how often such assessments need to be done. These analyses suggest two main conclusions: the interval between assessments can safely be longer than generally suggested, but this interval should depend on the assessed level of risk. Unless there is a clear trigger, such as starting smoking, major dietary change, or substantial weight gain, those at low initial cardiovascular risk can be reassessed in several years. Future guidelines should incorporate these findings and provide reassessment intervals stratified by initial cardiovascular risk.

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Contributors: KJLB conceived and designed the study, analysed and interpreted the data, and drafted and revised the manuscript. She is guarantor for the study. AH conceived and designed the study, analysed and interpreted the data, and revised the manuscript. LI, OT, and PG conceived and designed the study, interpreted the data, revised the manuscript, and obtained funding. SO analysed and interpreted the data and revised the manuscript. KJLB acquired a limited access dataset from the NHLBI and takes responsibility for the integrity of the data and the accuracy of the data analysis for the section of the paper pertaining to the Framingham Study.

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Ethical approval: This study was approved by the University of Sydney human research ethics committee (reference 05-2009/11855).

Data sharing: No additional data available.

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What is already known on this topic

Increasingly decisions to start blood pressure and lipid lowering treatment are based on an individual's absolute cardiovascular risk rather than blood pressure or cholesterol level, and individuals are regularly screened for increased risk

Optimal intervals for rescreening risk among those who do not initially qualify for treatment are uncertain

What this study adds

Remeasurement of cardiovascular risk may safely be done less frequently than recommended by most guidelines: 8-10 years for those initially at <10% risk of a cardiovascular event

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Tables

Table 1 | Baseline characteristics of two cohorts. Values are numbers (percentages) unless stated otherwise

| Characteristics | Tokyo health check-up (n=13 757) | Framingham study (n=3855) |
|---|----------------------------------|---------------------------|
| Men | 6533 (47.5) | 1590 (41.2) |
| Mean (SD) age (years) | 47.8 (9.8) | 45.7 (10.5) |
| Mean (SD) total cholesterol (mg/dL) | 204.0 (33.4) | 209.3 (40.1) |
| Mean (SD) HDL cholesterol (mg/dL) | 64.0 (15.9) | 53.3 (15.5) |
| Mean (SD) systolic blood pressure (mm Hg) | 115.8 (15.7) | 124.2 (15.6) |
| Smoker | 1318 (9.6) | 1427 (37.0) |
| Diabetes | 258 (1.9) | 71 (1.8) |
| Baseline risk: | | |
| <5% | 8342 (60.6) | 1762 (45.7) |
| 5-<10% | 3297 (24.0) | 1079 (28.0) |
| 10-<15% | 1409 (10.2) | 622 (16.1) |
| 15-<20% | 709 (5.2) | 392 (10.2) |

HDL=high density lipoprotein.

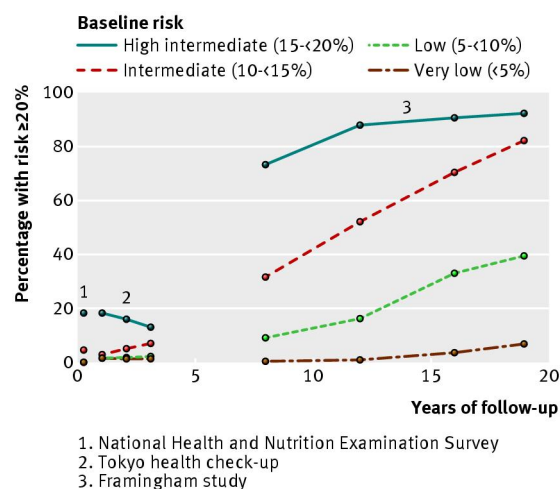
Table 2| Probability of crossing 20% cardiovascular disease risk threshold at increasing time intervals. Values are percentage of participants above threshold (95% confidence interval)

| Baseline risk | Years 1-3 (Tokyo health check-up) | | | Years 8-19 (Framingham study) | | | |
|---------------|-----------------------------------|-----------------------|----------------------|-------------------------------|----------------------|----------------------|----------------------|
| | 1 year | 2 years | 3 years | 8 years | 12 years | 16 years | 19 years |
| <5% | 0.0 (0.00 to 0.04) | 0.01 (0.00 to 0.07) | 0.05 (0.01 to 0.12) | 0.5 (0.2 to 1.0) | 1.0 (0.5 to 1.6) | 3.7 (2.8 to 4.9) | 6.8 (5.5 to 8.2)* |
| 5-<10% | 0.15 (0.05 to 0.35) | 0.43 (0.23 to 0.71) | 0.70 (0.45 to 1.05) | 9.1 (7.1 to 11.3)* | 16.4 (13.2 to 20.0)* | 33.2 (28.9 to 37.7)† | 39.7 (35.8 to 43.6)† |
| 10-<15% | 1.4 (0.9 to 2.2) | 3.6 (2.7 to 4.8) | 5.7 (4.5 to 7.0)* | 32.1 (27.6 to 36.8)† | 52.5 (45.0 to 59.9)† | 70.9 (63.3 to 77.7)† | 82.6 (77.4 to 87.0)† |
| 15-<20% | 16.1 (13.4 to 19.0)* | 14.0 (11.53 to 16.8)* | 11.3 (9.05 to 13.9)* | 73.5 (67.2 to 79.1)† | 88.4 (78.4 to 94.9)† | 91.2 (80.7 to 97.1)† | 92.8 (86.8 to 96.7)† |

*Moderate chance 5-20%.

†High chance >20%.

Figure



Probability of crossing 20% cardiovascular disease treatment threshold for 10 year cardiovascular event risk over 19 years of follow-up